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Anxiety Disorders: Noradrenergic Neurotransmission

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Abstract The past decade has seen a rapid progression in our knowledge of the neurobiological basis of fear and anxiety. Specific neurochemical and neuropeptide systems have been demonstrated to play important roles in the behaviors associated with fear and anxiety-producing stimuli. Long-term dysregulation of these systems appears to contribute to the development of anxiety disorders, including panic disorder, posttraumatic stress disorder (PTSD), and social anxiety disorder. These neurochemical and neuropeptide systems have been shown to have effects on distinct cortical and subcortical brain areas that are relevant to the mediation of the symptoms associated with anxiety disorders. Moreover, advances in molecular genetics portend the identification of the genes that underlie the neurobiological disturbances that increase the vulnerability to anxiety disorders. This chapter reviews clinical research pertinent to the neurobiological basis of anxiety disorders. The implications of this synthesis for the discovery of anxiety disorder vulnerability genes and novel psychopharmacological approaches will also be discussed.

Keywords Fear · Anxiety · Pathophysiology · Circuitry · Neurochemistry · Treatments

1 Neural Mechanisms of Anxiety and Fear

Classical fear conditioning is a form of associative learning in which subjects come to express fear responses to neutral conditioned stimuli (CS) that are paired with an aversive unconditioned stimulus (US). The CS, as a consequence of this pairing, acquire the ability to elicit a spectrum of behavioral, autonomic, and endocrine responses that normally would only occur in the context of danger (Blair et al. 2001). Fear conditioning can be adaptive and enable efficient behavior in dangerous situations. The individual who can accurately predict threat can engage in the appropriate behaviors in the face of danger. In the clinical situation, specific environmental features (CS) may be linked to a traumatic event, spontaneous panic attack, or embarrassing social situation (US), such that re-exposure to a similar environment produces a recurrence of symptoms of anxiety and fear. Patients often generalize these cues and experience a continuous perception of threat to the point that they become conditioned to context (Table 1 outlines the five neural mechanisms of anxiety and fear).

Cue-specific CS are transmitted to the thalamus by external and visceral pathways. Afferents then reach the lateral amygdala (LA) via two parallel circuits: a rapid subcortical path directly from the dorsal (sensory) thalamus and a slower regulatory cortical pathway encompassing primary somatosensory cortices, the insula, and the anterior cingulate/prefrontal cortex. Contextual CS are projected to the LA from the hippocampus and perhaps the bed nucleus of the stria terminalis. The long loop pathway indicates that sensory information relayed to the amygdala undergoes substantial higher level processing, thereby enabling assignment of significance, based upon prior experience, to complex stimuli. Cortical involvement in fear conditioning is clinically relevant because it provides a mechanism by which cognitive factors will influence whether symptoms are experienced or not, following stress exposure (LeDoux 2000).

During the expression of fear-related behaviors, the LA engages the central nucleus of the amygdala (CEA), which, as the principal output nucleus, projects to areas of the hypothalamus and brain stem that mediate the autonomic, endocrine, and behavioral responses associated with fear and anxiety (Schafe et al. 2001). The molecular and cellular mechanisms that underlie synaptic plasticity in amygdala-dependent learned fear is an area of very active investigation (Shumyatsky et al. 2002). Long-term potentiation (LTP) in the LA appears to be a critical mechanism for storing memories of the CS–US associa-

Table 1 Neural mechanisms related to pathophysiology and treatment of anxiety disorders

Mechanism	Neurochemical systems	Brain regions	Pathophysiology	Treatment development
Pavlovian (cue specific) fear conditioning	Glutamate, NMDA receptors, VGCCs	Medial prefrontal cortex, sensory cortex, anterior cingulate, dorsal thalamus, lateral amygdala, central nucleus of amygdala	May account for common clinical observation in panic disorder, PTSD that sensory and cognitive stimuli associated with or resembling the frightening experience elicit panic attacks, flashbacks, and autonomic symptoms	Treatment with NMDA receptor antagonist and VGCC antagonist may attenuate acquisition of fear
Inhibitory avoidance (contextual fear)	NE/β-adrenergic receptor, cortisol/glucocorticoid receptor, CRH, GABA, opioids, acetylcholine	Medial prefrontal cortex, basolateral amygdala, hippocampus, BNST entorhinal cortex	Excessive stress-mediated release of CRH, cortisol, and NE will facilitate development of indelible fear memories. Chronic anxiety and phobic symptoms may result from excessive contextual fear conditioning	CRH antagonists and β-adrenergic receptor agonists may have preventative effects
Reconsolidation	Glutamate, NMDA receptors, NE, β-adrenergic receptors, CREB	Amygdala, hippocampus	Repeated reactivation and reconsolidation may further strengthen the memory trace and lead to persistence of trauma and phobia-related symptoms	Treatment with NMDA receptor and β-adrenergic receptor antagonists after memory reactivation may reduce the strength of the original anxiety provoking memory
Extinction	Glutamate, NMDA receptors, VGCCs, NE, dopamine, GABA	Medial prefrontal sensory cortex, amygdala	Failure in neural mechanisms of extinction may relate to persistent traumatic memories, re-experiencing symptoms, autonomic hyperarousal, and phobic behaviors	Psychotherapies need to be developed that facilitate extinction through the use of conditioned inhibitors and the learning of "new memories" The combination of extinction based psychotherapy and D-cycloserine may be a particularly effective treatment
Sensitization	Dopaminergic, noradrenergic NMDA receptors	Nucleus accumbens, amygdala, striatum, hypothalamus	May explain the adverse effects of early life trauma on subsequent responses to stressful like events. May play a role in the chronic course of many anxiety disorders and, in some cases, the worsening of the illness over time	Suggests the efficacy of treatment may vary according to the state of evolution of the disease process. Emphasizes the importance of early treatment intervention

BNST, bed nucleus of the stria terminalis; CREB, cyclic AMP response element-binding protein; CRH, corticotrophin-releasing hormone; CS, conditioned stimuli; GABA, γ-aminobutyric acid; GCC, voltage-gated calcium channels; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; PAG, periaqueductal gray.

tion (Blair et al. 2001). A variety of behavioral and electrophysiological data has led LeDoux and colleagues to propose a model to explain how neural responses to the CS and US in the LA could influence LTP-like changes that store memories during fear conditioning. This model proposes that calcium entry through *N*-methyl-D-aspartate (NMDA) receptors and voltage gated calcium channels (VGCCs) initiates the molecular processes to consolidate synaptic changes into long-term memory (Blair et al. 2001). Short-term memory requires calcium entry only through NMDA receptors and not VGCCs.

This hypothesis leads to several predictions that may have relevance to the discovery of novel therapeutics for anxiety disorders. It suggests that blocking NMDA receptors in the amygdala during learning should impair short- and long-term fear memory. This has been demonstrated in rodents (Walker et al. 2000; Rodrigues et al. 2001). Valid human models of fear conditioning and the availability of the NMDA receptor antagonist memantine should permit this hypothesis to be tested clinically (Grillon 2002). If memantine impairs the acquisition of fear in humans, it may have utility in the prevention and treatment of anxiety disorders such as posttraumatic stress disorder (PTSD), and panic disorder. Blockade of VGCCs appears to block long-term but not short-term memory (Bauer et al. 2002). Therefore, clinically available calcium channel blockers such as verapamil and nimodipine may be helpful for in diminishing the intensity and impact of recently acquired fear memory and perhaps in preventing PTSD as well.

The discussion above has focused primarily upon the neural mechanisms related to the coincident learning of the US–CS association (i.e., Pavlovian fear conditioning) in the LA. However, there is significant evidence that a broader neural circuitry underlies fear memory that is modulated by amygdala activity. The inhibitory avoidance paradigm is used to examine memory consolidation for aversively motivated tasks and involves intentional instrumental choice behavior. Studies using inhibitory avoidance learning procedures have been used to support the view that the amygdala is not the sole site for fear learning; this view posits that the amygdala can modulate the strength of memory storage in other brain structures (McGaugh 2002).

Specific drugs and neurotransmitters infused into the basolateral amygdala (BLA) influence consolidation of memory for inhibitory avoidance training. Post-training peripheral or intra-amygdala infusions of drugs affecting γ-aminobutyric acid (GABA), opioid, glucocorticoid, and muscarinic acetylcholine receptors have dose- and time-dependent effects on memory consolidation (McGaugh 2002). Norepinephrine (NE) infused directly into the BLA after inhibitory avoidance training enhances memory consolidation, indicating that the degree of activation of the noradrenergic system within the amygdala by an aversive experience may predict the extent of the long-term memory for the experience (McIntyre et al. 2002).

Interactions among corticotropin-releasing hormone (CRH), cortisol, and NE have very important effects on memory consolidation, which is likely to be relevant to the effects of traumatic stress on memory. Extensive evidence indicates that glucocorticoids influence long-term memory consolidation via stimulation of glucocorticoid receptors (GR). The glucocorticoid effects on memory consolidation require activation of the BLA, and lesions of the BLA block retention enhancement of intrahippocampal infusions of a GR agonist. Additionally, the BLA is a critical locus of interaction between glucocorticoids and NE in modulating memory consolidation (McGaugh et al. 2002).

There is extensive evidence consistent with a role for CRH in mediating stress effects on memory consolidation. Activation of CRH receptors in the BLA by CRH released from the CEA facilitates stress effects on memory consolidation. Memory enhancement produced by CRH infusions in the hippocampus are blocked by propranolol, suggesting CRH, through a presynaptic mechanism, stimulates NE release in the hippocampus (Roozendaal et al. 2002).

These results support the concept that CRH via an interaction with glucocorticoids interacts with the noradrenergic system to consolidate traumatic memories. Individuals with excessive stress-induced release of CRH, cortisol, and NE are likely to be prone to the development of indelible traumatic memories and associated re-experiencing symptoms. Administration of CRH antagonists, glucocorticoid receptor antagonists, and β-adrenergic receptor antagonists may prevent these effects in vulnerable subjects.

2 Reconsolidation

Reconsolidation is a process in which old, reactivated memories undergo another round of consolidation (Debiec et al. 2002; Milekic et al. 2002; Myers et al. 2002). The process of reconsolidation is extremely relevant to both vulnerability and resiliency to the effects of extreme stress. It is the rule rather than the exception that memories are reactivated by cues associated with the original trauma. Repeated reactivation of these memories may serve to strengthen the memories and facilitate long-term consolidation (Przbyslawski et al. 1999; Sara 2000). Each time a traumatic memory is retrieved, it is integrated into an ongoing perceptual and emotional experience and becomes part of a new memory. Moreover, recent preclinical studies indicate that consolidated memories for auditory fear conditioning, which are stored in the amygdala (Nader et al. 2000a), hippocampal-dependent contextual fear memory (Debiec et al. 2002), and hippocampal-dependent memory associated with inhibitory avoidance (Milekic et al. 2002) are sensitive to disruption upon reactivation by administration with a protein synthesis inhibitor directly into the amygdala and hippocampus, respectively. The reconsolidation process, which has enormous clinical implications, results in reactivated memory trace that returns to a state of lability and must undergo consolidation once more if it is to remain in long-term storage. Some controversies persist regarding the temporal persistence of systems reconsolidation. Debiec and colleagues found that intrahippocampal infusions of anisomycin caused amnesia for a consolidated hippocampal-dependent memory if the memory was reactivated even up to 45 days after training (Debiec et al. 2002). Milekic and Alberini (2002), however, found that the ability of intrahippocampal infusion of anisomycin to produce amnesia for an inhibitory avoidance task was evident only when the memory was recent (up to 7 days). Further work is needed to resolve this very important question (Myers et al. 2002).

The reconsolidation process involves NMDA receptors, β-adrenergic receptors, and requires cyclic AMP response element binding protein (CREB) induction. The CREB requirement suggests that nuclear protein synthesis is necessary (Kida et al. 2002). NMDA receptor antagonists and β-receptor antagonists impair reconsolidation (Przbyslawski et al. 1997, 1999). The effect of the β-receptor antagonist propranolol was greater after memory reactivation than when administered immediately after initial training. These results suggest that reactivation of memory initiates a cascade of intracellular events that involve both NMDA receptor and β-receptor activation in a fashion similar to post-acquisition consolidation.

This remarkable lability of a memory trace, which permits a reorganization of an existing memory in a retrieval environment, provides a theoretical basis for both psychotherapeutic and pharmacotherapeutic intervention for traumatic stress exposure as well as other anxiety disorders. Administration of β-receptor and NMDA receptor antagonists shortly after trauma exposure or spontaneous panic attacks as well as after reactivation of memory associated with the anxiety-inducing event may reduce the strength of the original memory.

3 Extinction

When the CS is presented repeatedly in the absence of the US, a reduction in the condition fear response occurs. This process is called extinction. It forms the basis for exposure-based psychotherapies for the treatment of anxiety disorders characterized by exaggerated fear responses. Individuals who show an ability to quickly attenuate learned fear through a powerful and efficient extinction processes are likely to function more effectively under dangerous conditions.

Extinction is characterized by many of the same neural mechanisms as in fear acquisition. Activation of amygdala NMDA receptors by glutamate is essential (Myers and Davis 2004) and L-type VGCCs also contribute to extinction plasticity (Cain et al. 2002). Long-term extinction memory is altered by a number of different neurotransmitters systems including GABA, NE, and dopamine (DA) in a manner similar to fear acquisition (McGaugh et al. 1990; Willick et al. 1995).

Destruction of the medial prefrontal cortex (mPFC) blocks recall of fear extinction (Quirk et al. 2000; Morgan et al. 1993), indicating that the mPFC might store long-term extinction memory. Infralimbic neurons, which are part of the mPFC, fire only when rats are recalling extinction—greater firing correlates with reduced fear behaviors (Milad et al. 2002). It has been suggested that the consolidation of extinction involves potentiation of inputs into the mPFC by means of NMDA-dependent plasticity. The BLA sends direct excitatory inputs to the mPFC, and NMDA antagonists infused into BLA blocks extinction. The ability of the mPFC to modulate fear behaviors is probably related to projections from the mPFC via GABA interneurons to the BLA (Royer et al. 2000).

Failure to achieve an adequate level of activation of the mPFC after extinction might lead to persistent fear responses (Herry et al. 2002). Individuals with the capacity to function well following states of high fear may have potent mPFC inhibition of amygdala responsiveness. In contrast, patients with PTSD exhibit depressed ventral mPFC activity which correlated with increased autonomic arousal after exposure to traumatic reminders (Bremner et al. 1999). Consistent with this hypothesis, we recently showed that PTSD patients had increased left amygdala activation during fear acquisition and decreased mPFC/anterior cingulate activity during extinction (Bremner et al. 2003). It has been proposed that potentiating NMDA receptors using the glycine agonist, D-cycloserine, may facilitate the extinction process when given in combination with behavioral therapy in patients with anxiety disorders (Davis 2002).

These preclinical investigations suggest that clinical research paradigms capable of evaluating the mechanisms of fear conditioning in clinical populations would be of great value. Psychophysiological studies in PTSD patients have been reviewed recently and have consistently demonstrated increased electrophysiological and autonomic responses to trauma related stimuli (Orr et al. 2002). The startle reflex has been used to study fear conditioning in humans. Startle is a useful method for examining fear responding in experimental studies involving both animals and humans that is mediated by the amygdala and connected structures. There is evidence of elevation of baseline startle in almost all anxiety disorders (Grillon 2002), suggestive of increased contextual fear. This is consistent with hyperexcitability of neural structures underlying contextual fear such as the BNST. Vulnerability to anxiety disorders may relate to startle responses. Girls at high risk for developing anxiety disorders are overly sensitive to contextual threat, but exhibit normal fear-potentiated startle. High-risk boys, on the other hand, exhibit elevated potentiated startle and normal contextual responses. Cue fear learning is an adaptive process by which undifferentiated fear becomes cue specific. Deficits in cue fear learning may lead non-adaptive aversive expectancies and a state of chronic anxiety.

4 The Neurochemical Basis of Fear and Anxiety

Specific neurotransmitters and neuropeptides act on brain areas noted above in the mediation of fear and anxiety responses. These neurochemicals are released during stress, and chronic stress results in long-term alterations in function of these systems. Stress axis neurochemical systems prepare the organism for threat in multiple ways, through increased attention and vigilance, modulation of memory (in order to maximize the utilization of prior experience), planning, and preparation for action. In addition, these systems have peripheral effects, which include increased heart rate and blood pressure (catecholamines) and rapid modulation of the body's use of energy (cortisol). The neurobiological responses to threat and severe stress are clearly adaptive and have survival value, but they also can have maladaptive consequences when they become chronically activated. Examination of the preclinical data concerning neurochemical substrates of the stress response, the long-term impact of early life exposure to stress, and possible stress-induced neurotoxicity provide a context to consider clinical investigations of the pathophysiology of the anxiety disorders.

5 Noradrenergic System

Stressful stimuli of many types produce marked increases in brain noradrenergic function. Stress produces regional selective increases in NE turnover in the locus coeruleus (LC), limbic regions (hypothalamus, hippocampus, and amygdala), and cerebral cortex. These changes can be elicited with immobilization stress, foot-shock stress, tail-pinch stress, and conditioned fear. Exposure to stressors from which the animal cannot escape results in behavioral deficits termed learned helplessness. The learned helplessness state is associated with depletion of NE, probably reflecting the point where synthesis cannot keep up with demand. These studies have been reviewed elsewhere in detail (Bremner et al. 1996a,b).

The LC is a compact nucleus containing noradrenergic neurons as well as peptide neurotransmitters (e.g., hypocretin and CRH) that influence its activity. LC neurons can fire in either a tonic or phasic pattern, and electrotonic coupling between neurons can be influenced by neurotransmitters. Release of NE can be accompanied by co-release of the peptide neurotransmitter galanin, which is inhibitory and may alter the firing rate of DA neurons, thus altering its hedonic tone. Shifts in the pattern of firing of LC neurons are thought to be of great importance in understanding attentional processes, often disrupted in depression. The LC neurons have long dendritic processes for synaptic contact to influence its activity, and LC neurons may be strongly influenced by anterior cingulate cortex. It has recently been suggested that the A2 group of the medulla may innervate important structures such as the amygdala and nucleus accumbens and thus may be important in affect regulation. Receptors for NE are grouped into $\alpha 1$, $\alpha 2$, $\beta 1$, and $\beta 2$ subtypes.

Chronic therapy with antidepressants results in adaptive receptor alterations in the noradrenergic system. Three genes code for the expression of $\alpha 1$ subtypes, and these three receptor subtypes (A–C) have distinctive pharmacological properties. Recent data suggest that chronic antidepressants and electroconvulsive stimulation (ECS) may increase frontal cortex expression of mRNA specifically for the $\alpha 1$A-adrenoreceptor subtype and, as such, this receptor may be involved in the action of noradrenergic antidepressants (Nalepa et al. 2002). Repeated administration of antidepressants has been observed to increase behavioral responsivity to $\alpha 1$-adrenergic agonists (such as aggressiveness and hyperexploration) as well as increasing agonist-binding affinity for $\alpha 1$-adrenoreceptors.

Electrophysiological studies in the hippocampus also support enhanced $\alpha 1$ responses after chronic antidepressant treatments. Recent data indicate that the novel antidepressant tianeptine, which may increase serotonin reuptake when given chronically, also increases responsiveness of the $\alpha 1$-adrenergic system (Rogoz et al. 2001).

Single unit recording from the LC indicates that chronic administration of multiple classes of antidepressants and electroconvulsive stimulation reduce LC baseline and sensory-stimulated firing rates (Grant et al. 2001). It has been hypothesized that reducing the firing rate of noradrenergic neurons may be therapeutic, especially in anxiety disorders and also subgroups of patients with depression with certain clinical features, such as psychomotor retardation, by reducing the release of inhibitory co-released galanin neuropeptide onto DA neurons in the ventral tegmental area (VTA) (Weiss et al. 1998). However, reduced firing in the noradrenergic neurons of the LC could simply be a function of increased levels of synaptic or extracellular NE resulting in feedback inhibition of LC firing (Grant et al. 2001).

The $\alpha 2$ antagonist, yohimbine, has been observed to augment the speed of response to fluoxetine (Sanacora et al 2004), and in a very small study (n=14) of bipolar depression the $\alpha 2$ antagonist idazoxan appeared to have antidepressant effects equal to bupropion (Grossman et al 1999). Upregulation of immunolabeled $\alpha 2$A receptors and associated G proteins (Gi) are observed postmortem in suicide victims (Garcia-Sevilla et al. 1999). This is of interest, given the critical importance of these receptors in stress and in regulating levels of monoamines via autoreceptors and heteroreceptors. As well, the efficacy of antidepressants such as mirtazapine and mianserin may in part depend on these receptors. Recent transgenic experiments suggest that the $\alpha 2$ receptor may act as a "suppressor of depression," Knockout of the gene for the $\alpha 2$ receptor increases immobility in the forced swim test and eliminates the augmentation of forced swim test activity by imipramine (Schramm et al. 2001).

In contrast, other recent experiments suggest that mice lacking α2C receptors perform on the forced swim test in the *same* fashion as mice treated with antidepressants (Sallinen et al. 1999). Thus, the α2A and the α2C receptors may have complementary and opposing roles in the regulation of mood and anxiety and have a complementary role in NE responses in the heart (Schramm et al. 2001). If reducing α2C activity is to be used as an antidepressant strategy it may require some method of targeting only those receptors in the CNS, since an α2CDel322–325 polymorphism that reduces feedback inhibition of sympathetic NE released in the heart is associated a markedly a increased risk of heart disease (Small et al. 2002). Since some individuals with depression also have memory disturbance, recent evidence that mutation of the α2A receptor impairs working memory could also help us understand the cognitive symptoms observed in depression (Franowicz et al. 2002).

Crosstalk between the catecholamine system and steroids may be another novel mechanism through which NE and epinephrine—by increasing the sensitivity of glucocorticoid receptors to ligand activation—could alter mood and anxiety symptoms. A recent study found that amitriptyline prevented the appearance of impairment in spatial memory in aged rats and reduced glucocorticoid levels, and this effect is most likely secondary to NE-mediated alteration in glucocorticoid signaling (Yau et al. 2002). Augmentation effects of catecholamines on GR signaling may thus be important in cognitive and emotional processing. The PI3-K signaling pathway activation through β-receptors appears to be responsible for this putative enhancement of glucocorticoid activity, and it is tempting to conjecture that antidepressants that are known to downregulate β-receptors and influence PI3-K signaling could act by glucocorticoid receptor sensitization (Schmidt et al. 2001).

As can be seen in Table 2, chronic symptoms experienced by anxiety disorder patients, such as panic attacks, insomnia, startle, and autonomic hyperarousal, are characteristic of increased noradrenergic function (Charney et al. 1984, 1987a). Potential drugs of abuse, such as alcohol, opiates, and benzodiazepines (but not cocaine), decrease firing of noradrenergic neurons. Increases in abuse of these substances parallels increased anxiety symptoms, providing evidence for self-medication of these symptoms that is explainable based on animal studies of noradrenergic function. In addition, patients with anxiety disorders frequently report significant improvement of symptoms of hyperarousal and intrusive memories with alcohol, benzodiazepines, and opiates, which decrease LC firing, but worsening of these symptoms with cocaine, which increases LC firing.

There is strong evidence that function of the brain noradrenergic system is involved in mediating fear conditioning (Rasmussen et al. 1986; Charney and Deutch 1996). Neutral stimuli paired with shock (CS) produce increases in brain NE metabolism and behavioral deficits similar to those elicited by the shock alone (Cassens et al. 1981) as well as increased firing rate of cells in the LC (Rasmussen et al. 1986). An intact noradrenergic system appears

Table 2 Evidence for altered catecholaminergic function in anxiety disorders[a]

	PTSD	Panic disorder
Increased resting heart rate and blood pressure	+/–	+/–
Increased heart rate and blood pressure response to traumatic reminders/panic attacks	+ + +	+ +
Increased resting urinary NE and E	+	+/–
Increased resting plasma NE or MHPG	–	–
Increased plasma NE with traumatic reminders/panic attacks	+	+/–
Increased orthostatic heart rate response to exercise	+	+
Decreased binding to platelet α_2 receptors	+	+/–
Decrease in basal and stimulated activity of cAMP	+/–	+
Decrease in platelet MAO activity	+	NS
Increased symptoms, heart rate and plasma MHPG with yohimbine noradrenergic challenge	+ +	+ + +
Differential brain metabolic response to yohimbine	+	+

[a] One or more studies do not support this finding (with no positive studies), or the majority of studies does not support this finding; +/–, an equal number of studies support and do not support this finding; +, at least one study supports and no studies do not support the finding, or the majority of studies supports the finding; + +, two or more studies support and no studies do not support the finding; + + +, three or more studies support and no studies do not support the finding; cAMP, cyclic adenosine 3',5';-monophosphate; E, epinephrine; MAO, monoamine oxidase; MHPG, 3-methosy-4-hydroxyphenylglycol; NE, norepinephrine; NS, not studied; PTSD, posttraumatic stress disorder.

to be necessary for the acquisition of fear-conditioned responses (Cose and Robbins 1987).

Many patients with anxiety disorders experience an increased susceptibility to psychosocial stress. Behavioral sensitization may account for these clinical phenomena. In the laboratory model of sensitization, single or repeated exposure to physical stimuli or pharmacological agents sensitizes an animal to subsequent stressors (reviewed in Charney et al. 1993). For example, in animals with a history of prior stress, there is a potentiated release of NE in the hippocampus with subsequent exposure to stressors (Nisenbaum et al. 1991). Similar findings were observed in medial prefrontal cortex (Finlay and Abercrombie 1991). The hypothesis that sensitization is underlying neural mechanism contributing to the course of anxiety disorders is supported by clinical studies demonstrating that repeated exposure to traumatic stress is an important risk factor for the development of anxiety disorders, particularly PTSD (Table 1).

6 Posttraumatic Stress Disorder

There is extensive clinical evidence that NE plays a role in human anxiety. Well-designed psychophysiological studies have been conducted that have documented heightened autonomic or sympathetic nervous system arousal in combat veterans with chronic PTSD. Because central noradrenergic and peripheral sympathetic systems function in concert (Aston-Jones et al. 1991), the data from these psychophysiology investigations are consistent with the hypothesis that noradrenergic hyperreactivity in patients with PTSD may be associated with the conditioned or sensitized responses to specific traumatic stimuli.

There is some evidence that baseline levels of NE are consistently altered in combat-related PTDS. Women with PTSD secondary to childhood sexual abuse had significantly elevated levels of catecholamines (NE, epinephrine, DA) and cortisol in 24-h urine samples (Lemieux and Coe 1995). Sexually abused girls excreted significantly greater amounts of catecholamine metabolites, metanephrine, vanilmandelic acid, and homovanillic acid (HVA) than girls who were not sexually abused (DeBellis et al. 1994). Plasma levels of NE were elevated throughout a 24-h period collection period (Yehuda et al. 1995b) as were CSF levels of NE in PTSD patients (Baker et.al. 1997). In the latter case, exposure to traumatic reminders in the form of combat films resulted in increased epinephrine (McFall et al. 1992) and NE (Blanchard et al. 1991) release.

Studies of peripheral NE receptor function have also shown alterations in α2 receptor and cyclic adenosine 39,59-monophosphate (cAMP) function in patients with PTSD. Decreases in platelet adrenergic α2-receptor number (Perry et al. 1987), platelet basal adenosine, isoproterenol, forskolin-stimulated cAMP signal transduction (Lerer et al. 1987), and basal platelet monoamine oxidase (MAO) activity (Davidson et al. 1985) have been found in PTSD. These findings may reflect chronic high levels of NE release which lead to compensatory receptor down-regulation and decreased responsiveness.

Patients with combat-related PTSD compared to healthy controls had enhanced behavioral, biochemical, and cardiovascular responses to the α2 antagonist yohimbine, which stimulates central NE release (Southwick et al. 1993, 1997). Moreover, a positron emission tomography study demonstrated that PTSD patients have a cerebral metabolic response to yohimbine consistent with increased NE release (Bremner et al. 1997b).

7 Panic Disorder

There is considerable evidence that abnormal regulation of brain noradrenergic systems is also involved in the pathophysiology of panic disorder. Panic disorder patients are very sensitive to the anxiogenic effects of yohimbine in addition to having exaggerated plasma 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), cortisol, and cardiovascular responses (Charney et al. 1984, 1987a, 1992; Gurguis and Uhde 1990; Albus et al. 1992; Yeragani et al. 1992). Children with a variety of anxiety disorders exhibit greater anxiogenic responses to yohimbine than normal comparison children (Sallee et al. 2000). The responses to the α2-adrenergic receptor agonist clonidine are also abnormal in panic disorder patients. Clonidine administration caused greater hypotension, greater decreases in plasma MHPG, and less sedation in panic patients than in controls (Uhde et al. 1988; Nutt 1989; Coplan et al. 1995a,b; Marshall et al. 2002).

8
Phobic Disorders

Few studies have examined noradrenergic function in patients with phobic disorders. In patients with specific phobias, increases in subjective anxiety and increased heart rate, blood pressure, plasma NE, and epinephrine have been associated with exposure to the phobic stimulus (Nesse et al. 1985). This finding may be of interest from the standpoint of the model of conditioned fear, reviewed above, in which a potentiated release of NE occurs in response to a re-exposure to the original stressful stimulus. Patients with social phobia have been found to have greater increases in plasma NE in comparison to healthy controls and patients with panic disorder (Stein et al. 1992). In contrast to panic disorder patients, the density of lymphocyte α-adrenoceptors is normal in social phobic patients (Stein et al. 1993). The growth hormone response to intravenous clonidine (a marker of central α2-receptor function) is blunted in social phobia patients (Tancer et al. 1990).

9
Conclusion

There is emerging evidence that links the role of genetic factors to the vulnerability to stress-related psychopathology, such as PTSD. An investigation of twin pairs from the Vietnam Twin Registry reported that inherited factors accounted for up to 32% of the variance of PTSD symptoms beyond the contribution of trauma severity (True et al. 1993). The molecular neurobiological abnormalities that underlie these findings have not been elucidated. Two relatively small association studies which evaluated *D_2 dopamine receptor* polymorphisms in PTSD yielded contradictory results (Comings et al. 1996; Gelernter et al. 1999). A preliminary study found an association between the dopamine transporter (*DAT*) polymorphism and PTSD (Gelernter et al. 1999). Volumetric magnetic resonance imaging investigations demonstrated a smaller hippocampal volume in PTSD patients (Bremner et al. 1995; Bremner et al. 1997; Gurvits et al.

1996). A study of monozygotic twins discordant for trauma exposure found evidence that smaller hippocampal volume may constitute a risk factor for the development of stress-related psychopathology (Gilbertson et al. 2002). The recent identification of functional polymorphisms for the glucocorticoid receptor (DeRijk et al. 2002), the α2C adrenergic receptor subtype (Small et al. 2002), and for NPY synthesis (Kallio et al. 2001) provide opportunities to investigate the genetic basis of the neurochemical response patterns to stress.

Work is commencing to examine the genetic basis of the neural mechanisms of fear conditioning. There have been several recent advances in understanding the genetic contribution and molecular machinery related to amygdala-dependent learned fear. A gene encoding gastrin-releasing peptide (*Grp*) has been identified in the LA. The Grp receptor (GRPR) is expressed in GABAergic interneurons and mediates their inhibition of principal neurons. In GRPR knockout mice, this inhibition is reduced and LTP enhanced. These mice have enhanced and prolonged fear memory for auditory and contextual cues, indicating that the GRP signaling pathway may serve as an inhibitory feedback constraint on learned fear (Walker et al. 2000). The work further supports the role of GABA in fear and anxiety states (Goddard et al. 2001) and suggests the genetic basis of vulnerability to anxiety may relate to GRP, GRPR, and GABA (Ishikawa-Brush et al. 1997). Other preclinical studies indicate that there may be a genetically determined mesocortical and mesoaccumbens dopamine response to stress that relates to learned helplessness (Ventura et al. 2002). Recently, it was demonstrated that healthy subjects with the serotonin transporter polymorphism that has been associated with reduced 5-HT expression and function and increased fear and anxiety behaviors, exhibit increased amygdala neuronal activity in response to fear-inducing stimuli (Hariri et al. 2002; Garpenstrand et al. 2001; Holmes et al. 2002). These preclinical and clinical data suggest that multidisciplinary studies that use neurochemical, neuroimaging, and genetic approaches have the potential to clarify the complex relationships among genotype, phenotype, and psychobiological responses to stress.

References

Albus M, Zahn TP, Brier A (1992) Anxiogenic properties of yohimbine: behavioral, physiological and biochemical measures. Eur Arch Psychiatry Clin Neurosci 241:337–344

Aston-Jones G, Shipley MT, Chouvet G, Ennis M, VanBockstaele EJ, Pieribone V, Shiekhattar R (1991) Afferent regulation of locus coeruleus neurons: anatomy, physiology and pharmacology. Prog Brain Res 88:47–75

Baker DG, West SA, Orth DN, Hill KK, Nicholson WE, Ekhator NN, Bruce AB, Wortman MD, Keck PE, Geracioti JD (1997) Cerebrospinal fluid and plasma beta endorphin in combat veterans with post traumatic stress disorder. Psychoneuroendocrinology 22:517–529

Bauer EP, Schafe GE, LeDoux JE (2002) NMDA receptors and L-type voltage-gated calcium channels contribute to long-term potentiation and different components of fear memory formation in the lateral amygdala. J Neurosci 22:5239–5249

Blair HT, Schafe GE, Bauer EP, Rodrigues SM, LeDoux JE (2001) Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. Learn Mem 8:229–242

Blanchard EB, Kolb LC, Prins A, Gates S, McCoy GC (1991) Changes in plasma norepinephrine to combat-related stimuli among Vietnam veterans with post traumatic stress disorder. J Nerv Ment Dis 179:371–373

Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB (1995) MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry 152:973–981

Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS (1997) Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. Biol Psychiatry 41:23–32

Bremner JD, Krystal JH, Southwick SM, Charney DS (1996a) Noradrenergic mechanisms in stress and anxiety: I. Preclinical studies. Synapse 23:28–38

Bremner JD, Krystal JH, Southwick SM, Charney DS (1996b) Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. Synapse 23:39–51

Bremner JD, Innis RB, Ng CK, Staib L, Duncan J, Bronen R, Zubal G, Rich D, Krystal JH, Dey H, Soufer R, Charney DS (1997b) PET measurement of central metabolic correlates of yohimbine administration in posttraumatic stress disorder. Arch Gen Psychiatry 54:246–256

Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS (1999) Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biol Psychiatry 45:806–816

Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Staib LH, Soufer R, Charney DS (2003) Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. Biol Psychiatry 53:879–889

Cain C, Blouin A, Barad MG (2002) L-type voltage-gated calcium channels are required for extinction but not for acquisition or expression, of conditional fear in mice. J Neurosci 22:9113–9121

Cassens G, Kuruc A, Roffman M, Orsulak P, Schildkraut JJ (1981) Alterations in brain norepinephrine metabolism and behavior induced by environmental stimuli previously paired with inescapable shock. Behav Brain Res 2:387–407

Charney DS, Deutch A (1996) A functional neuroanatomy of anxiety and fear: implications for the pathophysiology and treatment of anxiety disorders. Crit Rev Neurobiol 10:419–446

Charney DS, Heninger GR, Breier A (1984) Noradrenergic function in panic anxiety: effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. Arch Gen Psychiatry 41:751–763

Charney DS, Woods SW, Goodman WK, Heninger GR (1987a) Neurobiological mechanisms of panic anxiety: biochemical and behavioral correlates of yohimbine-induced panic attacks. Am J Psychiatry 144:1030–1036

Charney DS, Deutch AY, Krystal JH, Southwick SM, Davis M (1993) Psychobiologic mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry 50:294–299

Comings DE, Muhleman D, Gysin R (1996) Dopamine D2 receptor (DRD2) gene and susceptibility to posttraumatic stress disorder: a study and replication. Biol Psychiatry 40:368–372

Coplan JD, Pine D, Papp L, Martinez J, Cooper T, Rosenblum LA, Gorman JM (1995a) Uncoupling of the noradrenergic-hypothalamic-pituitary adrenal axis in panic disorder patients. Neuropsychopharmacology 13:65–73

Coplan JD, Papp LA, Martinez MA, Pine P, Rosenblum LA, Cooper T, Liebowitz MR, Gorman JM (1995b) Persistence of blunted human growth hormone response to clonidine in fluoxetine-treated patients with panic disorder. Am J Psychiatry 152:619–622

Cose BJ, Robbins TW (1987) Dissociable effects of lesions to dorsal and ventral noradrenergic bundle on the acquisition, performance, and extinction of aversive conditioning. Behav Neurosci 101:476–488

Davidson J, Lipper S, Kilts CD, Mahorney S, Hammett E (1985) Platelet MAO activity in posttraumatic stress disorder. Am J Psychiatry 142:1341–1343

Davis M (2002) The role of NMDA receptors and MAP kinase in the amygdala in extinction of fear: clinical implications for exposure therapy. Eur J Neurosci 16:395–398

DeBellis MD, Lefter L, Trickett PK, Putnam FW (1994) Urinary catecholamine excretion in sexually abused girls. J Am Acad Child Adoles Psychiatry 33:320–327

Debiec J, LeDoux JE, Nader K (2002) Cellular and systems reconsolidation in the hippocampus. Neuron 36:527–538

DeRijk RH, Schaaf M, de Kloet ER (2002) Glucocorticoid receptor variants: clinical implications. J Steroid Biochem Mol Biol 81:103–122

Finlay JM, Abercrombie ED (1991) Stress induced sensitization of norepinephrine release in the medial prefrontal cortex. Soc Neurosci 17:151 (abstract)

Franowicz JS, Kessler LE, Borja CM, Kobilka BK, Limbird LE, Arnsten AF (2002) Mutation of the alpha2A-adrenoceptor impairs working memory performance annuls cognitive enhancement by guanfacine. J Neurosci 22:8771–8777

Garcia-Sevilla JA, Escriba PV, Ozaita A, La Harpe R, Walzer C, Eytan A, Guimon J (1999) Up-regulation of immunolabeled alpha2A-adrenoceptors Gi coupling proteins regulatory receptor kinases in the prefrontal cortex of depressed suicides. J Neurochem 72:282–291

Garpenstrand H, Annas P, Ekblom J, Oreland L, Fredrikson M (2001) Human fear conditioning is related to dopaminergic and serotonergic biological markers. Behav Neurosci 115:358–364

Gelernter J, Southwick S, Goodson S, Morgan A, Nagy L, Charney DS (1999) No association between D2 dopamine receptor (DRD2) "A" system alleles or DRD2 haplotypes, and posttraumatic stress disorder. Biol Psychiatry 45:620–625

Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5:1242–1247

Goddard AW, Mason GF, Almai A, Rothman DL, Behar KL, Petroff OA, Charney DS, Krystal JH (2001) Reductions in occipital cortex GABA levels in panic disorder detected with 1h-magnetic resonance spectroscopy. Arch Gen Psychiatry 58:556–561

Grant MM, Weiss JM (2001) Effects of chronic antidepressant drug administration electroconvulsive shock on locus coeruleus electrophysiologic activity. Biol Psychiatry 49:117–129

Grillon C (2002) Associative learning deficits increase symptoms of anxiety in humans. Biol Psychiatry 51:851–858

Grossman F, Potter W Z, Brown EA, Maislin GA (1999) Double-blind study comparing idazoxan and bupropion in bipolar depressed patients. J Affect Disord 56 237–43

Gurguis GNM, Uhde TW (1990) Plasma 3-methoxy-4 hydroxyphenylethylene glycol (MHPG) and growth hormone responses in panic disorder patients and normal controls. Psychoneuroendocrinology 15:217–224

Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarley W, Pitman RK (1996) Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biol Psychiatry 40:1091–1099

Hariri AR, Mattay VS, Tessitore A, Kolachana B, Fera F, Goldman D, Egan MF, Weinberger DR (2002) Serotonin transporter genetic variation and the response of the human amygdala. Science 297:400–403

Herry C, Garcia R (2002) Prefrontal cortex long-term potentiation but not long-term depression is associated with maintenance of extinction of learned fear in mice. J Neurosci 22:577–583

Holmes A, Yang RJ, Crawley JN (2002) Evaluation of an anxiety-related phenotype in galanin overexpresing transgenic mice. J Mol Neurosci 18:151–165

Ishikawa-Brush Y, Powell JF, Bolton P, Miller AP, Francis F, Willard HF, Lehrach H, Monaco AP (1997) Autism and multiple exostoses associated with an X-8 translocation occurring within the GRPR gene and 3′ to the SDC2 gene. Hum Mol Genet 6:1241–1250

Kallio J, Personen U, Kaipio K, Karvonen MK, Heinonen OJ, Uusitupa MI, Koulu M (2001) Altered intracellular processing and release of neuropeptide Y due to leucine 7 to proline 7 polymorphism in the signal peptide of preproneuropeptide Y in man. FASEB J 15:1242–1244

Kida S, Josselyn SA, de Ortiz SP, Kogan JH, Chevere I, Masushige S, Silva AJ (2002) CREB required for the stability of new and reactivated fear memories. Nat Neurosci 4:348–355

LeDoux JE (2000) Emotion circuits in the brain. Annu Rev Neurosci 23:155–184

Lemieux AM, Coe CL (1995) Abuse-related PTSD: evidence for chronic neuroendocrine activation in women. Psychosom Med 57:105–115

Lerer B, Ebstein RP, Shestatsky M, Shemesh Z, Greenberg D (1987) Cyclic AMP signal transduction in posttraumatic stress disorder. Am J Psychiatry 144:1324–1327

Marshall RD, Blanco C, Printz D, Liebowitz MR, Klein DF, Coplan J (2002) A pilot study of noradrenergic and HPA axis functioning in PTS vs. panic disorder. Psychiatry Res 110:219–230

McFall ME, Veith RC, Murburg MM (1992) Basal sympathoadrenal function in posttraumatic stress disorder. Biol Psychiatry 31:1050–1056

McGaugh JL (2002) Memory consolidation and the amygdala: a systems perspective. Trends Neurosci 25:456–461

McGaugh JL, Roozendaal B (2002) Role of adrenal stress hormones in forming lasting memory in the brain. Curr Opin Neurobiol 12:205–210

McGaugh JL, Castellano C, Brioni J (1990) Picrotoxin enhances latent extinction of conditioned fear. Behav Neurosci 104:264–267

McIntyre CK, Hatfield T, McGaugh JL (2002) Amygdala norepinephrine levels after training predict inhibitory avoidance retention performance in rats. Eur J Neurosci 16:1223–1226

Milad MR, Quirk GJ (2002) Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 420:70–74

Milekic MH, Alberini CM (2002) Temporally graded requirement for protein synthesis following memory reactivation. Neuron 36:521–525

Morgan MA, Romanski LM, LeDoux JE (1993) Extinction of emotional learning: contribution of medial prefrontal cortex. Neurosci Lett 163:109–113

Myers KM, Davis M (2002) Systems-level reconsolidation: re-engagement of the hippocampus with memory reactivation. Neuron 36:340–343

Myers KM, Davis M (2004) AX+, BX− discrimination learning in the fear-potentiated startle paradigm: possible relevance to inhibitory fear learning in extinction. Learn Mem 11:464–475

Nalepa I, Kreiner G, Kowalska M, Sanak M, Zelek-Molik A, Vetulani J (2002) Repeated imipramine electroconvulsive shock increase alpha(1A)-adrenoceptor mRNA level in rat prefrontal cortex. Eur J Clin Pharmacol 444:151–159

Nesse RM, Curtis GC, Thyer BA, McCann DS, Huber-Smith MJ, Knopf RF (1985) Endocrine and cardiovascular responses during phobic anxiety. Psychosom Med 47:320–332

Nisenbaum LK, Zigmund MJ, Sved AF, Abercrombie ED (1991) Prior exposure to chronic stress results in enhanced synthesis and release of hippocampal norepinephrine in response to a novel stressor. J Neurosci 11:1473–1484

Nutt DJ (1989) Altered alpha2-adrenoceptor sensitivity in panic disorder. Arch Gen Psychiatry 46:165–169

Orr SP, Metzger LJ, Pitman RK (2002) Psychophysiology of post-traumatic stress disorder. Psychiatr Clin North Am 25:271–293

Perry BD, Giller EL, Southwick SM (1987) Altered platelet alpha2 adrenergic binding sites in posttraumatic stress disorder. Am J Psychiatry 144:1511–1512

Przbyslawski J, Sara SJ (1997) Reconsolidation of memory after its reactivation. Behav Brain Res 84:241–246

Przbyslawski J, Roullet P, Sara SJ (1999) Attenuation of emotional and nonemotional memories after their reactivation: role of β adrenergic receptors. J Neurosci 19:6623–6628

Quirk GJ, Russo GK, Barron JL, Lebron K (2000) The role of ventral medial prefrontal cortex in the recovery of extinguished fear. J Neurosci 20:6225–6231

Rasmussen K, Marilak DA, Jacobs BL (1986) Single unit activity of the locus coeruleus in the freely moving cat. I. During naturalistic behaviors and in response to simple and complex stimuli. Brain Res 371:324–334

Rodrigues SM, Schafe GE, LeDoux JE (2001) Intra-amygdala blockade of the NR2B subunit of the NMDA receptor disrupts the acquisition but not the expression of fear conditioning. J Neurosci 21:6889–6896

Rogoz Z, Skuza G, Dlaboga D, Maj J, Dziedzicka-Wasylewska M (2001) Effect of repeated treatment with tianeptine fluoxetine on the central alpha(1)-adrenergic system. Neuropharmacology 41:360–368

Roozendaal B, Brunson KL, Holloway BL, McGaugh JL, Baram TZ (2002) Involvement of stress-released corticotrophin-releasing hormone in the basolateral amygdala in regulating memory consolidation. Proc Natl Acad Sci U S A 99:13908–13913

Royer S, Martina M, Pare D (2000) Bistable behaviour of inhibitory neurons controlling impulse traffic through the amygdala: role of a slowly deinactivating Kb current. J Neurosci 20:9034–9039

Sallee FR, Sethuraman G, Sine L, Liu H (2000) Yohimbine challenge in children with anxiety disorders. Am J Psychiatry 157:1236–1242

Sallinen J, Haapalinna A, MacDonald E, Viitamaa T, Lahdesmaki J, Rybnikova E, Pelto-Huikko M, Kobilka BK, Scheinin M (1999) Genetic alteration of the alpha2-adrenoceptor subtype c in mice affects the development of behavioral despair and stress-induced increases in plasma corticosterone levels. Mol Psychiatry 4:443–452

Sanacora G, Berman RM, Cappiello A, Oren DA, Kugaya A, Liu N, Gueorguieva R, Fasula D, Charney DS (2004) Addition of the alpha2-antagonist yohimbine to fluoxetine: effects on rate of antidepressant response. Neuropsychopharmacology 29:1166–1171

Sara SJ (2000) Retrieval and reconsolidation: toward a neurobiology of remembering. Learn Mem 7:73–84

Schafe GE, Nader K, Blair HT, LeDoux JE (2001) Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. Trends Neurosci 24:540–546

Schmidt P, Holsboer F, Spengler D (2001) Beta(2)-adrenergic receptors potentiate glucocorticoid receptor transactivation via G protein beta gamma-subunits and the phosphoinositide 3-kinase pathway. Mol Endocrinol 15:553–564

Schramm NL, McDonald MP, Limbird LE (2001) The alpha(2a)-adrenergic receptor plays a protective role in mouse behavioral models of depression and anxiety. J Neurosci 21:4875–4882

Shumyatsky G, Tsvetkov E, Malleret G, Vronskaya S, Horton M, Hampton L, Battey JF, Dulac C, Kandel ER, Bolshakov VY (2002) Identification of a signaling network in lateral nucleus of amygdala important for inhibiting memory specifically related to learned fear. Cell 111:905–918

Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB (2002) Synergistic polymorphisms of β1and α2c adrenergic receptors the risk of congestive heart failure. N Engl J Med 347:1135–1142

Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolaou A, Heninger GR, Charney DS (1993) Abnormal noradrenergic function in posttraumatic stress disorder. Arch Gen Psychiatry 50:266–274

Southwick SM, Krystal JH, Bremner JD, Morgan CA, Nicolaou A, Nagy LM, Johnson DR, Heninger GR, Charney DS (1997) Noradrenergic and serotonergic function in posttraumatic stress disorder. Arch Gen Psychiatry 54:749–758

Stein MB, Tancer ME, Uhde TW (1992) Heart rate and plasma norepinephrine responsivity to orthostatic challenge in anxiety disorders. Comparison of patients with panic disorder and social phobia and normal control subjects. Arch Gen Psychiatry 49:311–317

Stein MB, Huzel LL, Delaney SM (1993) Lymphocyte b-adrenoceptors in social phobia. Biol Psychiatry 34:45–50

Tancer ME, Stein MB, Uhde TW (1990) Effects of thyrotropin-releasing hormone on blood pressure and heart rate in phobic and panic patients: a pilot study. Biol Psychiatry 27:781–783

True WR, Rice J, Eisen SA, Heath AC, Goldberg J, Lyons MJ, Nowak J, (1993) A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch Gen Psychiatry 50:257–264

Uhde T, Joffe RT, Jimerson DC, Post RM (1988) Normal urinary free cortisol and plasma MHPG in panic disorder: clinical and theoretical implications. Biol Psychiatry 23:575–585

Ventura R, Cabib S, Puglisi-Allegra S (2002) Genetic susceptibility of mesocortical dopamine to stress determines liability to inhibition of mesoaccumbens dopamine and to behavioral despair in a mouse model of depression. Neuroscience 115:99–1007

Walker DL, Davis M (2000) Involvement of NMDA receptors within the amygdala in short-versus long-term memory for fear conditioning as assessed with fear-potentiated startle. Behav Neurosci 114:1019–1033

Weiss JM, Bonsall RW, Demetrikopoulos MK, Emery MS, West CH Galanin (1998) A significant role in depression? Ann N Y Acad Sci 863:364–382

Willick ML, Kokkinidis L (1995) Cocaine enhances the expression of fear-potentiated startle: evaluation of state-dependent extinction and the shock-sensitization of acoustic startle. Behav Neurosci 109:929–938

Yau JL, Noble J, Hibberd C, Rowe WB, Meaney MJ, Morris RG, Seckl JR (2002) Chronic treatment with the antidepressant amitriptyline prevents impairments in water maze learning in aging rats. J Neurosci 22:1436–1442

Yehuda R, Boisoneau D, Lowy MT, Giller EL Jr (1995b) Dose response changes in plasma cortisol and lymphocyte glucocoriticooid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. Arch Gen Psychiatry 52:583–593